A systems genetics approach to analyze the biological response to low dose radiation

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An understanding of the genetic basis of individual variation in responses to the deleterious effects of radiation is a prerequisite for identification of high risk individuals, as well as for the development of novel strategies for prevention of tissue damage and tumor therapy. We are investigating the contribution of non-targeted effects to the low dose radiation response using female murine strains with variable radioresponse (Balb/C and Spretus). We report here our preliminary results measuring changes in serum cytokines and metabolites in a time course after 10 cGy irradiation. Our goal is to use these phenotypes to predict the risk of radiation-induced tumorigenesis.

We have started to characterize the two parental strains. We have irradiated mice from both strains with 10 cGy and then harvested serum in a time-course out 5 days after exposure. Our hypotheses are: (1) that genetics controls gene network- and ECM-component profiles, (2) that these profiles differentially regulate targeted and untargeted stress responses, and (3) that Spretus is more resistant to low dose-induced oxidative stress than Balb/C.

Our early results indicate that there are strain-dependent differences in serum cytokines and metabolomic profiles in untreated mice with Balb/C showing relatively higher expression than Spretus. The cytokines show perturbations in a time course after exposure to a single 10 cGy X-ray dose with more changes in Balb/C than in Spretus. Spretus shows more rapid recovery to low dose-induced stress. Future work will examine persistence of these changes at a longer time course after radiation exposure. In addition we will characterize the blood cell distribution to evaluate recruitment of migrating hematopoietic cells in parental mouse strains before and after 10 cGy Xrays. We will also characterize F1 and F1-Backcrosss cytokine and metabolomic profile and blood cell distributions in a dose response from 10 cGy to 100 cGy. This comprehensive systems biology approach may identify specific genes or pathways that are differentially controlled between mouse strains, and contribute to variation in susceptibility to radiation-induced carcinogenesis.

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